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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/924,011	DEPHILLIPO ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-38* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Election/Restrictions

Applicant's response filed on 08/07/01 has been acknowledged.

Claims 39-56 are canceled.

Claims 1-38 are pending.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***703-872-9306****.*

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-38, drawn to a method of assessing relative susceptibility of a human to an undesirable bone density condition, the method comprising assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group consisting genes which encode a protein component of bone matrix classified in class 435, subclass 6.

II. Claims 1-38, drawn to a method of assessing relative susceptibility of a human to an undesirable bone density condition, the method comprising assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group genes which encode an enzyme that catalyzes synthesis of an organic component of bone matrix classified in class 435, subclass 6.

III. Claims 1-38, drawn to a method of assessing relative susceptibility of a human to an undesirable bone density condition, the method comprising assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group consisting genes which encode an enzyme that catalyzes deconstruction of an organic component of bone matrix classified in class 435, subclass 6.

IV. Claims 1-38, drawn to a method of assessing relative susceptibility of a human to an undesirable bone density condition, the method comprising

assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group consisting genes which encode a protein that facilitates mineralization of bone matrix classified in class 435, subclass 6.

V. Claims 1-38, drawn to a method of assessing relative susceptibility of a human to an undesirable bone density condition, the method comprising assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group consisting genes which encode a protein that facilitates de-mineralization of bone matrix classified in class 435, subclass 6.

VI. Claims 1-38, drawn to a method of assessing relative susceptibility of a human to an undesirable bone density condition, the method comprising assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group consisting genes which encode a protein that influences, by way of a transmembrane signaling pathway of a bone cell classified in class 435, subclass 6.

VII. Claims 1-38, drawn to a method of assessing relative susceptibility of a human to an undesirable bone density condition, the method comprising assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group consisting genes which encode a protein associated with vitamin D uptake or with vitamin D metabolism classified in class 435, subclass 6.

VIII. Claims 1-38, drawn to a method of assessing relative susceptibility of a human to an undesirable bone density condition, the method comprising assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group consisting genes which encode a protein for which the level of expression of the protein is associated with bone erosion classified in class 435, subclass 6.

IX. Claims 1-38, drawn to a method of assessing relative susceptibility of a human to an undesirable bone density condition, the method comprising assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group consisting genes which encode a protein for which the level of expression of the protein is associated with bone resorption classified in class 435, subclass 6.

X. Claims 1-38, drawn to a method of assessing relative susceptibility of a human to an undesirable bone density condition, the method comprising assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group consisting genes which encode a protein for which the level of expression of the protein is associated with bone formation classified in class 435, subclass 6.

The inventions are distinct, each from the other because of the following reasons:

Inventions I-X are distinct. Inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case a) genes which encode a protein component of bone matrix; b) genes which encode an enzyme that catalyzes synthesis of an organic component of bone matrix; c) genes which encode an enzyme that catalyzes deconstruction of an organic component of bone matrix; d) genes which encode a protein that facilitates mineralization of bone matrix; e) genes which encode a protein that facilitates de-mineralization of bone matrix; f) genes which encode a protein that influences, by way of a transmembrane signaling pathway of a bone cell, expression of a protein selected from the group consisting of i) a component of bone matrix; ii) an enzyme that catalyzes synthesis of an organic component of bone matrix; iii) an enzyme that catalyzes deconstruction of an organic component of bone matrix; iv) a protein that facilitates mineralization of bone matrix;

and v) a protein that facilitates de-mineralization of bone matrix; g) genes which encode a protein associated with vitamin D uptake or with vitamin D metabolism; h) genes which encode a protein for which the level of expression of the protein is associated with bone erosion; i) genes which encode a protein for which the level of expression of the protein is associated with bone resorption; and j) genes which encode a protein for which the level of expression of the protein is associated with bone formation have different structure, modes of operation, functions and effects. For example genes which encode a protein that facilitates mineralization of bone matrix are structurally and functionally distinct from genes which encode a protein that facilitates de-mineralization of bone matrix. In addition, search of a polynucleotide ending a specific gene is not required for other genes as claimed. Therefore there exists a serious search burden to examine all the groups is one single invention. Thus these inventions are distinct and are of separate uses.

In addition groups I-X further encompasses various independent and distinct Inventions, which are distinct form each other. In order to be perfectly clear, the following Inventions within the particular Groups are NOT species elections. These are independent and distinct Inventions for the reasons given below and a further election of a single Invention from the elected Group is required.

With regard to Groups I-X above the independent and distinct Inventions are as follows:

1. *the gene which encodes parathyroid hormone (PtH);*
2. *a gene which encodes a PtH receptor;*
3. *the gene which encodes calcitonin;*
4. *a gene which encodes a calcitonin receptor;*
5. *a gene which encodes a vitamin D receptor;*
6. *the gene which encodes osteocalcin;*
7. *the gene which encodes tumor necrosis factor-alpha 1;*

8. *a gene which encodes a tumor necrosis factor-alpha 1 receptor;*
9. *the gene which encodes transforming growth factor beta;*
10. *the gene which encodes the alpha 1 subunit of type 1 collagen;*
11. *a gene which encodes an estrogen receptor;*
12. *the gene which encodes interleukin-6;*
13. *a gene which encodes an interleukin-6 receptor;*
14. *the gene which encodes bone morphogenic protein;*
15. *the gene which encodes apolipoprotein E;*
16. *the gene which encodes vitamin D 1 alpha-hydroxylase;*
17. *the gene which encodes insulin-like growth factor 1;*
18. *the gene which encodes the calcium sensing receptor of parathyroid gland cells;*
19. *the gene which encodes aromatase cytochrome P-450.*

Inventions 1-19 as listed above are distinct. Inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case each gene as mentioned above has different structure and function, which would have different effects on bone formation. For example defect in bone density due to modulation of estrogen receptor would be different than modulation of bone density by interleukin-6 gene product. Thus the identification of each gene in the modulation of bone density is distinct in its own context.

With regard to Groups VI specifically the corresponding independent and distinct Inventions are as follows:

A. genes which encode a protein component of bone matrix
B. genes which encode an enzyme that catalyzes synthesis of an organic component of bone matrix
C. genes which encode an enzyme that catalyzes deconstruction of an organic component of bone matrix
D. genes which encode a protein that facilitates mineralization of bone matrix

E. genes which encode a protein that facilitates de-mineralization of bone matrix

Inventions A-E as listed above are distinct. Inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case each gene as mentioned above has different structure and function, which would have different effects on bone formation (supra). Thus the identification of each gene in the modulation of bone density is distinct in its own context.

With regard to Groups 1-19 above the corresponding independent and distinct Inventions are as follows:

a) *occurrence of a cytosine residue in the codon of the gene encoding transforming growth factor beta 1 protein corresponding to amino acid residue 10 of the protein, whereby the codon encodes proline;*

b) *occurrence of a thymine residue 8 residues upstream of the normal start codon of the gene encoding vitamin D receptor, whereby the residue is part of an initiation codon and the gene encodes a variant vitamin D receptor comprising three additional amino acids at its amino terminus;*

c) *occurrence of a nucleotide residue that is characteristic of apolipoprotein E polymorphic variant 4;*

d) *occurrence of a thymine residue in the gene encoding the alpha 1 subunit of type 1 collagen at a site at which a guanine residue normally occurs, whereby a recognition site for the transcription factor Sp1 is altered;*

e) *occurrence of a cytosine residue at position -174 of the interleukin 6 gene promoter;*

f) *occurrence of guanine residue at the position at which a cytosine residue normally occurs in the codon corresponding to amino acid residue 986 of the calcium sensing receptor gene, whereby the codon encodes a serine residue;*

g) *occurrence of a thymine residue at the position corresponding to position +1417 of the cDNA encoding a PtH receptor;*

h) *occurrence of a thymine residue at the position at which a cytosine residue normally occurs in the codon corresponding to amino acid residue 447 of the calcitonin receptor gene, whereby the codon encodes a leucine residue;*

i) *occurrence of a thymine residue at position +1377 of the calcitonin receptor gene; and*

j) *occurrence of a cytosine residue where a guanine residue normally occurs at the first nucleotide position of intron 2 of the PtH gene.*

k) *occurrence of a thymine-adenine repeat at position -1174 upstream of exon 1 of the estrogen receptor gene.*

l) *occurrence of a tetranucleotide simple tandem repeat in intron 4 of the aromatase cytochrome P-450 gene.*

m) *occurrence of a cytosine-adenine repeat at a position from 947 to 984 residues upstream of the transcription start site of the insulin growth factor 1 gene*

Inventions a)-m) as listed above are distinct. Inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case each gene as mentioned above has different structure and function, which would have different effects on bone formation. For example defect in bone density due to modulation of estrogen receptor would be different than modulation of bone density by interleukin-6 gene product. Thus the identification of polymorphism in each gene in the modulation of bone density is distinct in its own context.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, and the

literature and sequence searches for each Group would be divergent from another Group, so restriction for examination purposes as indicated is proper.

In addition with regard to the different Inventions, the burden of search exists since a different search is required for each gene, related SNP or haplotype, especially in context with its role in bone density conditions. For example, in order to properly a particular gene, its SNP or haplotype will need to be searched in the Registry file of STN, and in the computer database maintained by the STIC and will also require individualized searching in published documents which disclose polymorphisms in the genes as claimed. Since the review of such information would be different for each gene, SNP-site and haplotype, there exists a serious search burden to examine all the groups as one single invention.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to ***(571) 272-0547.***

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306.**

Sumesh Kaushal
Examiner Art Unit 1636

SUMESH KAUSHAL
PATENT EXAMINER